THE COMMISSIONER OF PATENTS
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IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

Applicant: S Lukas et al Examiner: Alysia Berman

Serial No.: 09/177,427

Title: Taste Masked Pharmaceutical Compositions

DECLARATION UNDER 37 C.F.R. Sl. 132

Hon. Commissioner of Patents
and Trade Marks
Washington, DC 20231

Sir,

I, Stefan Lukas, declare and say as follows:

1. I am an inventor of the subject matter claimed in the above-identified U S patent application Serial No. 09/177,427.

2. I hold a Masters in Applied Science from the University of South Australia which was conferred in 1988. I have worked for F H Faulding & Co Limited since April 1988. I was first involved in spray drying in 1988 with what was at the time a minor research project looking at microencapsulation using a lab-scale spray dryer. As part of this program I developed the basic polymer coating process and formulation from concept to pilot scale manufacture eventually using pilot equipment on site at Niro Atomiser, Soborg, Denmark. After two separate visits to the pilot facility in Denmark two different formulations were successfully scaled up and taken through to commercial reality.

3. I identified the critical formulation constraints not previously described in the literature. During more than 8 years continuous hands on experience in all aspects of spray drying micro encapsulation I thoroughly investigated raw material specifications/requirements, requirements of coating systems, atomisation (including evaluation of numerous atomisation techniques both physical and electrostatic), evaluated the drying environment and the importance of the composition and physical attributes of the drying gas.

4. I also liaised with an extra mural team at Particle Coating Technologies (PCT) in St Louis, Missouri in the development of a taste masking process that involved spray congealing of molten wax compositions. In this process the active actually dissolved in the molten wax producing a different kind of spray dried microencapsulated particle. I have read extensively in the area and have attended several drying symposia.

5. I have read and am familiar with the Office Action mailed 8 May, 2001, in respect of application Serial No. 09/177,427, and make this Declaration in support of the patentability of the claims in the above-identified application.

6. As set forth in the specification of the application, Serial No. 09/177,427 and as recited in the claims, the invention is directed towards a taste masked pharmaceutical composition. The claimed composition has a number of properties, one property is that the polymer coating comprises less than 23% by weight of the formulation. A further property is that the core has an aspect ratio of less than 3. A final property included within the claims is the fact that the particle

size is controlled within a prescribed range so that only a certain percentage of particles are present as 'large' or 'fine' particles. I note that no more than 25% w/w of particles are less than 25 micrometres and no more than 2% w/w of particles are over 250 micrometres. As also described, the invention further relates to a method of preparing a formulation of the invention comprising spray drying powder particles with a suitable aspect ratio to produce a formulation with acceptable properties.

7. I note in the Office Action that the Examiner is of the opinion that the limitations of the aspect ratio of less than 3 (as enclosed in claim 16) and/or the substantially spherical nature of the core (as disclosed in claim 19) is not considered critical and does not render the claims patentable over the prior art.

8. Whilst I understand how the Examiner could reach this position, I respectfully disagree with this view on the basis of my research toward the invention.

9. An important feature of the particles of the present invention is the particle shape. In developing the claimed process, a number of trial batches were run in order to produce a pharmaceutical composition with acceptable product qualities. We had observed, for example, that when the process of CA2068366 was carried out, some of the batches appeared to be acceptable whereas other were clearly unacceptable. We therefore wanted to conduct research to improve the consistency of the product produced.

10. In tests to determine the critical factors, we particularly looked at a number of variables such as particle size and particle shape. Merely by way of overview, we noted that where there was a high occurrence of "fine" drug particles, there was an increased rate of drug released after polymer coating. Whilst not wishing to be bound by theory, we thought that the smaller particles increased the drug surface area which in turn, led to a thinner polymer coating. At least in a theoretical manner, one can easily see that if there is a great number of drug particles that are too small, the surface area to drug ratio with be high, leading to a thinner coating. Accordingly, whilst the process works with fine particle, it is preferable that the size of the particles be controlled within a certain range. My recollection in developing this process is that it was this observation that led to the limitation that appears as a preferred embodiment in claims 20 and 21 of the present application.

11. With respect to particle shape, we conducted a number of tests to determine if particle shape affects the process of invention as it was not expected to. These tests were predominantly influenced by the observation that with certain batches, unacceptable taste masking was observed whereas with certain other batches, taste masking was adequate. Indeed, our review of literature in this area provided no indication as to what caused this variation. Indeed, we noted when running the process of the cited prior art documents, that some batches appeared to produce acceptable results whereas others were unacceptable.

12. Whilst a number of trials were run to determine the source of this variation, two spring immediately to mind. I have reviewed my files and have located test batches D4426 and D4427. Attached as Exhibit 1, is a Scanning Electron Micrograph (SEM) of the drug particles used in test D4426. Attached as Exhibit 2, is a SEM of the drug particles used in test D4427. These two materials were then subjected to the spray drying process using identical amounts of solvent and identical process conditions.

13. The test results demonstrate that there was significant difference between the dissolution rates of the two batches. The batch containing needles (i.e. an aspect ratio in excess of 3), was tested and observed that 18% of the material was released after 40 minutes. For the purpose of sustained release, this was found to be a less preferred dissolution profile. In contrast, using the material with an aspect ratio of less than 3, only 6% was released after 40 minutes. Accordingly, we were able to ascertain that the presence of "needle" shaped particles led to unacceptably high rates of drug release. Whilst not wishing to be bound by theory, I am of the opinion that the higher

release rate can be explained by the increased surface area inherent in a needle particle and possibly also, the tendency of premature breaking of the polymer coat at the vertices of these particles (where the polymer coating would be thinner and under greater stress).

14. In essence, drug release from a coated particle is dependent on the thickness and quality of the polymer coating. In turn, the thickness of the polymer coating is dependent on the specific surface area of the drug particles to be coated. We have found that the specific surface area is controlled within acceptable boundaries to give acceptable sustained release profiles by increasing the particle size and reducing the aspect ratio (as claimed in the application). In addition, this minimises the stress fractures that appear to be deleterious to the integrity of the coating layer. Accordingly, I consider that the combination of particle size distribution and aspect ratio of the material to be coated is crucial to acceptable produce performance. In addition, as far as I am aware, prior to the experimental work done, this was not a known feature of this process.

15. I have read, and am familiar with, CA2068366. I note, as acknowledged by the Examiner, that no particular shape is given in this citation. It does not appear to me that the authors were aware of the crucial nature of the shape of the particles and the particle size distribution at the time of the filing. It is for this reason that this document does not disclose the importance of the aspect ratio or shape.

16. I have read and am familiar with US 4,808,411. Once again, as noted by the Examiner, this reference does not disclose the crucial feature of the shape of the particle. This is not surprising as as stated previously, this was not known at the time of the publication.

17. Accordingly, I consider the present invention to contain patentable matter over and above the disclosure in the cited prior art. I consider that the determination of a suitable aspect ratio, shape and particle size distribution that guarantees acceptable taste masking and sustained released properties to be a patentable invention over the art. A worker following the directions in the art, would at best, only have a chance of reproducibly producing an acceptable product. This would only occur if the worker were fortuitously to select a core material with suitable aspect ratios and particle size distribution. The advance provided by the present application is that a worker can now proceed with certainty to achieve a product with acceptable product performance. By providing teachings that allow a skilled addressee to determine whether this performance will be achieved, the present inventors have provided for greater product output and better compliance with drug dissolution profiles. Accordingly, I consider there is a patentable advance and disagree with the Examiner on this point.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements are made with the knowledge that wilful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Act, and that such wilful false statements may jeopardise this application or any patent issuing thereon.

Dated 1/11/01

Stefan Lukas